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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,634	11/25/1997	ELAZAR RABBANI	ENZ-53(DIV-2	4640

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ENZO DIAGNOSTICS, INC.
C/O ENZO BIOCHEM INC.
527 MADISON AVENUE 9TH FLOOR
NEW YORK, NY 10022

EXAMINER	
SCHMIDT, MARY M	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/25/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/978,634	RABBANI ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-281* is/are pending in the application.

4a) Of the above claim(s) *254,265,278 and 279* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-2253, 255-264, 266, 277, 280, 281* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *31* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Drawings

1. The drawings dated 11-25-97 are objected to and corrections are required according to the PTO-948 mailed with the previous Office action on 12/03/02.

Claim Objections

2. Claim 260 has a typographical error in line 3 and improper Markush language. The "[and" needs to be deleted and the "or" replaced with and prior to the phrase "a combination thereof."

Election/Restriction

3. Applicant's election with traverse of (1) Monomeric units are attached to a binding matrix for claim 245; (2) Linear for claims 245, 246 and 257; (3) heteropolymer for claims 245, 247 and 258; (4) virus for claims 249 and 250; (5) recombinantly produced compound for claims 245, 251 and 259; (6) protein for claims 245 and 252; (7) receptor binding protein for claims 245, 252 and 253; (8) polyclonal for claims 245, 252, 253 and 254; (9) linear for claims 245, 252 and 255; (10) polynucleotide for claims 245 and 260; (11) combination of ionic interaction, hydrogen bonding and dipole-dipole interactions for claims 245 and 261; (12) polycationic and polyanionic interactions for claims 245, 261, 262, 280 and 281; (13) heterogeneous for claims 245 and 265-266; (14) polynucleotide for claim 275; (15) antibody for claims 275, 276 and 277 in Paper No.

31, filed 1/8/03, is acknowledged. The traversal is on the ground(s) that "Although 35 U.S.C. 121 provides that restriction may be required to one or two or more independent and distinct inventions, 37 C.F.R. 1.141 provides that a reasonable number of species may still be claimed in one application if the other conditions of the rule are met. Applicants note that in groups (2), (3), (8), (9), (12) or (13) there are only two species recited, in groups (1), and (15) there are only three species recited. It would certainly not be unduly burdensome to search such a small and limited number of species. Furthermore, the species in each of the specified groups are related to each other. Specifically, the claims in (1) are directed to RNA processing elements and the claims in group (2) are directed to the nucleic acid product. Applicants respectfully request, therefore, that the rejection be withdrawn." This is not found persuasive because although applicant asserts that the number of species is relatively small and that the species are all related, the combination of all the different species as claimed has not been taken into account by applicant. Furthermore, the species are so broad in themselves (ie. for example, the species polynucleotide and antibody) that the search burden for each is not specific and distinct since each species would require a broad search due to the quantity of literature associated with each species. Furthermore, the species in claim 252, for example, include a protein (class 530, subclass 300 or 350) or a polynucleotide (class 536, subclass 23.1). These class are highly divergent and the search for both would be considered an undue burden for claim 252.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 254, 265, 278 and 279 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 30.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 252, 253, 255 and 256 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 252 lacks antecedent basis for the limitation "said analyte-specific moiety" since the parent claim 245 does not have this limitation. Claims 253, 255 and 256 are further included in the instant rejection for their dependency on claim 252.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 245-253, 255-264 and 266-277 and 280-281 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 245 is drawn to a multimeric complex composition comprising more than one monomeric unit, said monomeric unit comprising a compound and polymer and wherein said monomeric units are attached to a binding matrix comprising a polymer through noncovalent polymeric interactions between said polymer of said monomeric unit and said polymer of said binding matrix. Claim 246 specifies wherein the polymeric interactions of said monomeric unit are linear. Claim 247 specifies wherein the polymer or oligomer of said monomeric unit comprises heteropolymer. Claim 248 specifies wherein said monomeric unit comprises an analyte-specific moiety. Claim 249 specifies wherein said analyte-specific moiety is capable of recognizing a component in a biological system. Claim 250 specifies wherein said biological system is a virus. Claim 251 specifies wherein the monomeric unit is selected from the group consisting of a recombinantly produced compound. Claim 252 specifies wherein the analyte-specific moiety is a protein. Claim 253 specifies wherein the protein is a receptor binding protein. Claim 255 specifies wherein the polynucleotide is linear. Claim 256 specifies wherein the polynucleotide is single-stranded. Claim 257 specifies wherein the polymer or oligomer of said binding matrix is linear. Claim 258 specifies wherein the polymer or oligomer of said binding matrix comprises a heteropolymer. Claim 259 specifies wherein the binding matrix is a recombinantly produced compound. Claim 260 specifies wherein the binding matrix comprises a polynucleotide. Claim 261 specifies a combination of ionic interactions, hydrogen bonding and

dipole-dipole interactions as the polymeric interactions. Claim 262 specifies that the ionic interaction of claim 261 are a combination of polycationic and anionic interactions. Claim 263 specifies that an entity is attached to the binding matrix. Claim 264 specifies that the entity is a ligand or a compound which increased binding of the binding matrix. Claim 266 specifies that the composition of claim 245 is in heterogeneous form. Claim 280 specifies wherein said monomeric unit contains polycationic segments and the binding matrix contains polyanionic segments. Claim 281 specifies wherein the monomeric unit contains polyanionic segments and the binding matrix contains polycationic segments.

Claim 275 is drawn to a mulitmeric composition comprising more than one component attached noncovalently to a charged polymer, wherein said charged polymer is a polynucleotide. Claim 276 specifies wherein the multimeric composition comprises a protein. Claim 277 specifies that the multimeric composition is an F(ab')2 fragment.

Claim 267 is drawn to a process for delivering a cell effector to a cell, comprising providing the multimeric complex composition of claim 245 wherein the monomeric unit comprises said cell effector and administering said composition. Claim 268 specifies that the delivery is *in vivo*. Claim 269 specifies that the delivery is *ex vivo*. Claim 270 specifies that the cell is contained in an organism.

Claim 271 is drawn to a process for delivering a gene or fragment thereof to a cell, comprising providing the multimeric complex composition of claim 245, wherein said monomeric unit comprises said gene or gene fragment; and administering said composition.

Claim 272 specifies that the composition is delivered *in vivo*. Claim 273 specifies that the composition is delivered *ex vivo*. Claim 274 specifies that the cell is contained in an organism.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

By way of specific design and example, vectors for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data in the specification as filed. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught

where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The instantly claimed compositions and the methods of delivery of those compositions are considered to lack written description in the specification as filed for a representative number of species of any such composition because the text of the specification as filed provides only general guidance, and not specific guidance, for the design and use of the claimed compounds. The U1-antisense compounds (summarized above) are not considered representative of the genus of instantly claimed mulitmeric complex compositions comprising a monomeric unit of a compound and a polymer where the binding matrix is a polymer through noncovalent polymeric

interaction between the polymer of the monomeric unit and polymer of the binding matrix. The U1-antisense cassette vectors do not have noncovalent polymeric interactions. Even though they are composed entirely of polynucleotides in the form of a vector, the polynucleotide units in the U1-cassette vectors are covalently bound to each other.

From the figures and the prophetic examples in the specification as filed, one of skill in the art would not be able to readily envisage a representative number of specific examples of the claimed multimeric complexes. Pages 69-80 of the instant specification discuss prophetically the types of multimeric complexes considered by the applicant. The description therein is very broad and does not provide a clear picture of specific species that can be readily envisaged by one of skill in the art to have a particular structure which correlates to a specific function.

Absent further specific guidance as to the exact structure of the claimed compositions, but reference to the specific interactions between the component of the multimeric complex, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of any such multimeric complex as broadly claimed.

Response to Arguments

9. Applicant's arguments filed 06/12/2002 have been fully considered but they are not persuasive.

Applicants state on page 10 of the response filed 06/12/2002 that "an adequate description has been provided. A detailed description of the multimeric complexes and

compositions of the present invention. Additionally, the term "monomeric units" and "polymeric interactions" are also clearly defined. In particular, as noted above, A sufficiently detailed description is provided in the specification for obtaining the mulitmeric complexes of the present invention on pages 69-80. Working examples are provided in Examples 16-18. This include the preparation of a multimeric antibody, preparation of multimeric insulin by hybridization and by hybridization to discrete sequences. These are illustrated in Figures 21, 22 and 23."

However, in the election of species, applicant elected for claim 275 a polynucleotide (and not an antibody) as the charged polymer that is attached non-covalently to the multimeric composition. Independent claim 245 also is drawn to multimeric complex compositions comprising more than one monomeric unit comprising a compound and polymer attached to a binding matrix comprising a polymer through noncovalent polymeric interactions between the polymers of each of the monomeric unit and the binding matrix. Thus, the examples cited by applicant of the preparation of a multimeric antibody and preparation of multimeric insulin (a protein) by hybridization to discrete sequences does not provide a representative number of species of any possible "compound", "polymer" or "component" of instant claims 245 and 275 and their dependent claims. The specification as filed teaches on page 79, last paragraph, that "[t]hese multicomplex compounds could further contain many other entities as ligands, receptors, chemical modifications that either enhance their biological function, increase their solubility, provide further cooperative overall binding or provide capability to bind to desired cells *in vitro* and *in vivo*. Thus another aspect of this invention is the composition, described above, further

comprising an entity attached to the binding matrix. Such an entity can comprise a ligand or a compound which increases the binding of the binding matrix. Examples of such entities are the cellular matrix proteins (fibronectin), lectins, polysaccharides, and polycationic polymers such as polylysine and histones." This description is very broad and does not provide specific clarity as to how the compound is structured when complete. This excerpt provides broad statements on how to make the putative multicomplex compounds, but doesn't provide a sufficient nexus between how they are made, and what they look like upon completion. As such, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of any such compound (or the methods of using such compounds) at the time the invention was made.

Applicant further argues on pages 10-11 of the response filed 6/12/02 that figures 21, 22 and 23 provide written description support for the claims. However, these figures are illustrations that are not representative of the breath of compounds claimed. Example 16 correlates to Figures 19 and 20 according to the description in example 16. Example 17 correlates to figure 22, but the polyT-insulin complex is not considered to be representative of the breath of compounds, polymers and components instantly claimed. Example 18, which correlates to figure 23, is drawn to use of single-stranded bacteriophage M13 nucleic acid sequences that are artificially synthesized with a primary amino group on the nucleotide at the 5' end and this activated and attached to insulin as described in Figure 17.

While these figures do show some types of compounds and multimeric compositions, it is not clear what additional features and substitutions may be made in the exemplified constructs in order to make a representative number of species of any such composition as broadly claimed. The claims as written are broadly drawn, and the specification does not further clarify specifically a representative number of species. As such, one of skill in the art would not readily recognize that applicant was in possession of the invention as claimed.

10. Claims 267-274 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing a nucleic acid product in a whole organism (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 267 is drawn to a process for delivering a cell effector to a cell, comprising providing the multimeric complex composition of claim 245 wherein the monomeric unit comprises said cell effector and administering said composition. Claim 268 specifies that the delivery is *in vivo*. Claim 269 specifies that the delivery is *ex vivo*. Claim 270 specifies that the cell is contained in an organism.

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monomeric unit comprises said gene or gene fragment; and administering said composition. Claim 272 specifies that the composition is delivered *in vivo*. Claim 273 specifies that the composition is delivered *ex vivo*. Claim 274 specifies that the cell is contained in an organism.

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parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

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Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in

examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Although the instant claims 267-274 do not specifically state that the nucleic acids in the multimeric compositions are antisense nucleic acids, the figures 21-23 cited by applicant as representative of the instant claimed invention contain single-stranded nucleic acids which hybridize to other nucleic acids by complementary sequence binding and thus function equivalently to an antisense oligonucleotide composition. Thus, the claims as written, which involve administration of these antisense compounds to cells in a whole organism, have a high level of unpredictability in the art analogous to that in the antisense field.

There is a high level of unpredictability known in the antisense art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." When expressed from a vector, the antisense must retain the ability to be localized to the target area. Thus use of U1 introns in the examples in the specification as filed are helpful

for targeting the antisense expressed to the nucleus of the cell, but the unpredictability remains for factors such as expression levels of the antisense, the localization of the vector to desired tissues, and expression of the antisense for the recited function, inhibition of the target gene. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach

that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecule containing complexes *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification

nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule constructs *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

11. Applicant's arguments filed 06/12/02 have been fully considered but they are not persuasive.

Note that the previous rejection of the composition claims (instant claims 245-253, 254-264, 266, 275-277, and new claims 280-281, are not included in the instant rejection since the reduction to practice of one enbodiment is considered representative for enablement purposes of the claimed compositions.

In regards to the Branch and Flanagan references previously cited and reiterated above pertaining to the unpredictability in the art of administration of antisense compounds to cells in a whole organism, applicant argues that they "were actually published after the priority date of the

above-referenced application. The MPEP 2164.05(a) states that "the state of the prior art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date reference to demonstrate that the patent is no-enabling.""

In response, the Branch, Flanagan and other newly cited references above are relied upon to teach that even today, there is a high level of unpredictability in the art for design and use of antisense in whole organisms due to the complexity of the whole organism environment and the number of unpredictable factors argued above.

Applicants further "assert that there are a number of publications available as of the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al., 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences."

In response, the Liu et al. article is a publication of the constructs and experiments taught in the instant specification. However, the Liu et al. paper does not further provide any *in vivo* context of use for the disclosed constructs. While they state on page 4085 that "[t]he choice of U1 as an antisense carrier provided structural stability and nuclear localization", they further state

that "[t]his successful approach in cell culture is being developed as means of achieving a high level of stable resistance in patent cells for the purpose of developing an ex vivo therapy for treating HIV infections." Thus, the *in vivo* uses are "being developed" and were not show at the time the invention was made to function *in vivo*. The Crook reference does not further provide an specific expectation of success for the instantly disclosed constructs to function *in vivo* either.

Applicant further states that "It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." However, Applicants note that clinical trials were being conducted by the assignee of the instant application around its priority date (Exhibit 4). The results have been favorable and a number of public announcements have been made concerning the ongoing clinical trials and results."

The above rejection does not imply that an animal model of a disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to a make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 4 does not teach what constructs are in trials and whether or not they function as instantly claimed in the context of a whole organism.

Applicants further state that "as conceded by the Office action, Applicants have demonstrated the penetration of cells by the antisense compounds, notably antisense inhibition of HIV in infected U937 cell culture. Therefore, the question of penetration of the plasma membrane of target cells should not be an issue." In response, the rejection is not a scope of enablement rejection which states that use of the claimed compounds in cells in cell culture is enabled. However, this example is not representative of uses in a whole organism for the reasons stated above.

Lastly, "Applicants note that specificity to any degree and certainly 100% specificity is not required of any drug under the patent laws and is evaluated on a case-by-case basis by the Food and Drug Administration. For example, penicillin is known to be far from specific to a certain target protein of harmful bacteria. However, this does not diminish the importance of penicillin as a useful drug." In response, the issues surrounding penicillin are not analogous to nucleic acid therapeutic compounds such as antisense-type compounds which have a different set of criteria for making and using in a whole organism. While the specification does not need to show that 100% of the claimed invention embodiments are enabled for use at the time the invention was made, the specification does need to overcome the unpredictability in the art with specific direction or guidance as to how to make and use the claimed invention. As put forth above, for the breath of the claimed invention, there is a high level of unpredictability in the art, from which one of skill in the art would necessarily practice an undue amount of experimentation to make and use.

Claim Rejections - 35 USC § 102

12. Claims 245-251, 257-264, 266, 267, 271, 275-277 and 280-281 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al. (U.S. Patent 5,521,291) for the same reasons of record as set forth in the previous Official actions mailed 02/17/99, 11/09/99 and 12/19/00.

Claim 245 is drawn to a multimeric complex composition comprising more than one monomeric unit, said monomeric unit comprising a compound and polymer and wherein said monomeric units are attached to a binding matrix comprising a polymer through noncovalent polymeric interactions between said polymer of said monomeric unit and said polymer of said binding matrix.

Curiel et al. teach in figure 1 combination of plasmid DNA and an antibody/polylysine complex and an adenovirus. They teach in col. 4, lines 29-40, that figure 1 is a "[d]iagrammatic representation of adenovirus-poly-cation-DNA complexes containing a foreign epitope on the adenovirus capsid. To accomplish this linkage of an adenovirus and a polycationic DNA-binding domain, the chimeric adenovirus P202-Ad5 containing a heterologous epitope in the exterior domain of its hexon protein was employed in conjunction with the monoclonal antibody MP301 specific for this epitope. The monoclonal antibody was rendered competent to carry foreign DNA sequences by attaching a polylysine moiety. Interaction of the polylysine-antibody complexed DNA with adenovirus P202-Ad5 occurs via the specificity of the conjugated

antibody." In figure 5 (col. 5, lines 1-6) they taught administration of this complex to cells in cell culture.

Claim 246 specifies wherein the polymeric interactions of said monomeric unit are linear. Claim 257 specifies wherein the polymer or oligomer of said binding matrix is linear. Since it is unclear what part of the monomeric unit is linear, the relationship between the polylysine and the antibody to polylysine is depicted as linear (in a straight line) in figure 1 of Curiel et al.

Claim 247 specifies wherein the polymer or oligomer of said monomeric unit comprises heteropolymer. Claim 258 specifies wherein the polymer or oligomer of said binding matrix comprises a heteropolymer. The nucleic acid polymer (the plasmid DNA) in figure 1 of Curiel et al. is heteropolymer (more than one unit of nucleic acid). Claim 266 specifies that the composition of claim 245 is in heterogeneous form. Since "hetero" simply means different, the different compounds in the Curiel et al. Figure 1 embrace instant claim 266.

Claim 248 specifies wherein said monomeric unit comprises an analyte-specific moiety. The instant specification teaches on page 70 what is meant by "analyte specific". Curiel et al. teaches in figure 1 both a plasmid DNA and an antilysine antibody that are polynucleotides and antibodies considered on page 70 of the instant specification as analyte-specific moieties. Claim 249 specifies wherein said analyte-specific moiety is capable of recognizing a component in a biological system. The antipolylysine antibody is capable of recognizing the polylysine. Claim 250 specifies wherein said biological system is a virus. The figure 1 depiction of Curiel et al. shows that the antibody also interacts with the adenovirus.

Claim 251 specifies wherein the monomeric unit is selected from the group consisting of a recombinantly produced compound. Claim 259 specifies wherein the binding matrix is a recombinantly produced compound. The plasmid DNA in figure 1 of Curiel et al. is recombinantly produced.

Claim 260 specifies wherein the binding matrix comprises a polynucleotide. The plasimid DNA of figure 1 of Curiel et al. is a polynucleotide.

Claim 261 specifies a combination of ionic interactions, hydrogen bonding and dipole-dipole interactions as the polymeric interactions. It is inherent that the interactions between the double-strands of DNA in the plasmid DNA of figure 1 of Curiel et al. are hydrogen bonded since it was known in the art at the time the invention was made that this is how nucleic acids interact to form the double helix. Furthermore all buffered solutions of plasmid DNA, antibodies and polylysine would have ionic interactions and dipole-dipole interactions as a function of the chemical reactions among these compounds. Claim 262 specifies that the ionic interaction of claim 261 are a combination of polycationic and anionic interactions. The description of figure 1, col. 4, further states that the DNA complexes are made of polycation DNA. Although it was not specifically mentioned that the complexes of DNA/polylysine/antibody and adenovirus had anionic interactions, it was inherent that anionic interactions were taking place in the buffer. Claim 280 specifies wherein said monomeric unit contains polycationic segments and the binding matrix contains polyanionic segments. Claim 281 specifies wherein the monomeric unit contains polyanionic segments and the binding matrix

contains polycationic segments. Since the limitations in the claims, "monomeric unit" and "binding matrix" are so ubiquitous in nature, these terms could be considered to take into account the same constructs. For example, figure 1 of Curiel et al. could be interpreted in two ways: (1) where the adenovirus is the binding matrix, and the antibody polylysine complex is the monomeric unit, or (2) where the monomeric unit is the adenovirus and the antibody polylysine complex is the binding matrix. Since the polycationic DNA is positively charged, any negatively charged elements in the buffer or the adenovirus that it interacts with would full-fill the claimed anionic interaction consideration.

Claim 263 specifies that an entity is attached to the binding matrix. Claim 264 specifies that the entity is a ligand or a compound which increased binding of the binding matrix. An epitope was attached to the adenovirus for binding the monoclonal antibody bound DNA (col. 21, lines 32-34).

Claim 275 is drawn to a multimeric composition comprising more than one component attached noncovalently to a charged polymer, wherein said charged polymer is a polynucleotide. Claim 276 specifies wherein the multimeric composition comprises a protein. Claim 277 specifies that the multimeric composition is an F(ab')2 fragment.

Claim 267 is drawn to a process for delivering a cell effector to a cell, comprising providing the multimeric complex composition of claim 245 wherein the monomeric unit comprises said cell effector and administering said composition. Curiel et al. taught in col. Col. 5, figure 5, the administration of their complex to HeLa cells in cell culture.

Claim 271 is drawn to a process for delivering a gene or fragment thereof to a cell, comprising providing the multimeric complex composition of claim 245, wherein said monomeric unit comprises said gene or gene fragment; and administering said composition. Curiel et al. taught in col. Col. 5, figure 5, the administration of their complex (including a plasmid with a gene sequence) to HeLa cells in cell culture.

13. Claims 268-270 and 272-274 are considered free of the prior art since the closest prior art

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader,* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

M. M. Schmidt
March 24, 2003